

The Risks and Benefits of Cannabis in the Dermatology Clinic

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Abstract

Cannabis (*Cannabis sativa/indica*), also known as marijuana, has been used for medicinal and recreational purposes for millennia. There has been a recent trend to legalize the use of cannabis, as illustrated by the recent legalization votes in numerous states in the United States and legislation in Canada to allow recreational cannabis use. With this increasing consumption of cannabis, dermatologists will see increased pressure to prescribe cannabis and will see the side effects of cannabis use with greater frequency. There are several approved medical indications for cannabis use, including psoriasis, lupus, nail-patella syndrome, and severe pain. In addition, very preliminary studies have suggested cannabis and its derivatives might have use in acne, dermatitis, pruritus, wound healing, and skin cancer. Further well-controlled studies are required to explore these potential uses. Conversely, the side effects of cannabis use are relatively well documented, and dermatologists should be aware of these presentations. Side effects of cannabis use include cannabis allergy manifesting as urticaria and pruritus, cannabis arteritis presenting with necrosis and ulcers, and oral cancers from cannabis smoke. In this review, we summarize some of the studies and reports regarding the medicinal uses of cannabis in the dermatology clinic and some of the side effects that might present more often to dermatologists as the use of cannabis increases.

Keywords

Cannabis, medical marijuana, psoriasis, pain, acne, dermatitis, arteritis, allergy, cancer

Cannabis (*Cannabis sativa/indica*), also known as marijuana, use has been increasing amongst patients who use it to treat a variety of diseases and conditions. In addition, there have been a growing number of countries and states in the United States that have legalized recreational cannabis use. Recreational cannabis is legal in California, Colorado, Nevada, Oregon, Alaska, and Washington, as well as in the Netherlands and Uruguay. Several other states and Canada are in the process of decriminalizing cannabis and allowing legal recreational use. Medical cannabis is widely accepted in Canada, most European countries, Australia, and numerous states in the United States. Cannabis and its derivatives have been approved for medical use for a variety of conditions that dermatologists might see in the clinic (Table 1).¹⁻³ Here, we review the current and potential medical uses of cannabis in the dermatology clinic and discuss the potential cutaneous side effects of cannabis use that will present with increasing frequency to the dermatologist.

Cannabis Use as a Dermatological Therapeutic

The major active compound of cannabis, Δ^9 -tetrahydrocannabinol (THC), is thought to mainly exert its clinical effects as an agonist of cannabinoid receptors 1 and 2 (CB1 and CB2, respectively). These receptors have

endogenous ligands and are found throughout the skin.⁴ The potential therapeutic use of cannabis is complicated by the fact that signaling through CB1 and CB2 can have opposite effects.⁵ Furthermore, non-THC phytocannabinoids found in cannabis, such as cannabidiol (CBD) and Δ^9 -tetrahydrocannabivarin, can act as CB1 antagonists and may modulate the effect of THC.⁶

Currently Approved Medical Cannabis Indications

Overall, there is a relative paucity of direct evidence regarding the treatment of skin disease with medical marijuana, even in the approved indications. In nail-patella syndrome, we identified a single case report of a patient who smoked cannabis and subjectively found that he had less pain, muscle spasms, and nausea.⁷ For neurofibromatosis, we were able to identify only a case series of 2 patients with pilocytic

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Table 1. Dermatologic Indications for Medical Marijuana by State in the United States.

Dermatologic Indication	Approved State(s)
Severe pain	Alaska, Arizona, Arkansas, Colorado, Connecticut, Delaware, Hawaii, Maine, Maryland, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Ohio, Oregon, Pennsylvania, Rhode Island, Vermont, Washington
Lupus	Illinois, New Hampshire
Nail-patella syndrome	Illinois, Michigan, Maine
Neurofibromatosis	Illinois
Psoriasis	Connecticut

astrocytomas, in children without neurofibromatosis. Both patients had subtotal excisions of their tumors but then saw regression of the tumors over many years during which they happened to smoke marijuana.⁸ In terms of the indication for lupus, we identified a poster of a 5-year longitudinal cohort study that found that cannabis use did not reduce pain, narcotic analgesia use, or systemic lupus erythematosus disease activity.⁹ Finally, the indication in psoriasis appears based on an in vitro study that found that various cannabinoids were able to inhibit keratinocyte proliferation in a nonpsoriasis model.¹⁰ We were unable to identify any studies with psoriasis.

The treatment of pain with medical marijuana has greater evidence and may warrant consideration in patients with painful conditions, such as hidradenitis suppurativa. There have been several randomized controlled trials¹¹⁻¹⁴ and a meta-analysis to determine the efficacy of smoking cannabis in treating neuropathic pain.¹⁵ This meta-analysis demonstrated that the number needed to treat was 5.6 patients to reduce chronic pain by greater than 30%.¹⁵ The treatment of acute pain with medical marijuana has had mixed results. Studies on postoperative pain showed no benefit from the use of 2 oral synthetic cannabinoids, dronabinol and nabilone.^{16,17} An intramuscular synthetic cannabinoid, levonantradol, showed no benefit for postoperative pain or pain secondary to trauma.¹⁸ Conversely, a multicenter study of cannabis plant extract for postoperative pain found a dose-dependent reduction in pain.¹⁹ Pain remains the most widely accepted indication for medical marijuana.¹⁻³

Potential Future Medical Cannabis Indications

Acne. The potential use of cannabis and its extracts in the treatment of acne has been controversial. In a study of 11 healthy males followed over 12 weeks, a cream containing 3% cannabis seed extract was compared with the vehicle, with regard to sebum production and erythema of the cheeks. They found a significant reduction in sebum production and

erythema.²⁰ The study is limited by the fact that there was only single blinding, and the subjects did not have active acne. In an in vitro study using immortalized sebocytes and full-thickness human skin organ culture, it was demonstrated that anandamide increased lipid production, while CBD was able to counteract this effect.²¹ Anandamide is an endogenous cannabinoid, which like THC is a cannabinoid receptor agonist. CBD, as discussed above, is thought to be a CB1 antagonist. Furthermore, a survey of French youth showed higher rates of cannabis use among those with moderate to severe acne.²² Taken together, these studies appear to be conflicting, as one would expect the major component of the cannabis seed extract to be THC, a cannabinoid receptor agonist, which should have increased the sebum production.

Eczematous Eruptions. The studies of cannabis and its extracts in the treatment of eczematous eruptions have shown some promise, but the interpretation of the studies is limited by the lack of good controls. A mouse model of allergic contact dermatitis showed positive results for the ability of topical and systemic THC to reduce the inflammatory response. Furthermore, knock-out mice for both CB1 and CB2 receptors show exaggerated allergic contact dermatitis.²³ Interestingly, CB2-specific agonists were ineffective or exaggerated the response, and CB2 antagonists helped reduce the response.²³⁻²⁵ N-palmitoyl ethanolamine enhances the effect of cannabinoid agonists and has been studied in eczematous dermatitis in human subjects. In an uncontrolled, open-label, observational study of 22 patients with prurigo, lichen simplex chronicus, and pruritus treated with a topical cream containing N-palmitoyl ethanolamine, 14 patients were found to have a good antipruritic effect.²⁶ In a larger second uncontrolled, open-label, observational study of patients with moderate to severe atopic dermatitis, subjects were found to have decreases in the signs and symptoms of eczema.²⁷ Unfortunately, neither study had a vehicle control arm; thus, these results are difficult to interpret. Furthermore, in a study comparing the N-palmitoyl ethanolamine cream to a competing moisturiser, there was no statistically significant difference in transepidermal water loss and current perception threshold. The study did claim significant reductions in scaling, dryness, and pruritus in the group using the moisturiser containing N-palmitoyl ethanolamine; however, this moisturiser also varied in many other constituents compared to the comparative moisturiser.²⁸ Aliamide is a CB1 and CB2 receptor agonist but also acts through vanilloid receptors. An uncontrolled study showed improvement in 80% of patients with topical application of aliamide.²⁹ Again, there was no vehicle control and, as such, further studies are required to validate these findings.

Cholestatic Pruritus. Reported in a single case series, 3 patients with cholestatic pruritus were treated at a starting dose of 5 mg of THC (dronabinol) by mouth. All 3 patients had failed at least ursodeoxycholic acid, cholestyramine, rifampin, and plasmapheresis. Two of the patients found 4 to

6 hours of relief from pruritus per dose, and the other found 2 to 3 hours of relief.³⁰

Wound Healing. Studies have shown that the CB2 receptor is expressed by numerous cells during the wound healing process. In a recent study using a mouse model of wound healing, a CB2 agonist was found to decrease the inflammatory response and fibrosis. Furthermore, there was quicker re-epithelization.³¹ The implication of this study is that CB2 agonists might limit scar formation and promote faster wound closure.

Systemic Sclerosis. Systemic sclerosis results in fibrosis of tissues that can include the skin. Bleomycin injection in mice is used as an experimental model of fibrosis. Mice that were CB2 knockouts had increased dermal thickness compare to wild-type mice when exposed to bleomycin. Furthermore, wild-type mice treated with a CB2 agonist treated with bleomycin showed a decreased inflammatory response and decreased dermal thickening.³² Ajulemic acid is a synthetic THC analog without psychotropic effects. It is an agonist of CB1 and CB2 but is also an agonist of PPAR- γ . Signaling through the PPAR- γ pathway is anti-fibrotic. Mice exposed to ajulemic acid were resistant to dermal fibrosis secondary to bleomycin injection. If mice were treated with ajulemic acid part way through the course of bleomycin, further fibrosis was halted, but there was no reversal of preexisting fibrosis. Furthermore, mice with constitutively active TGF β -I receptors are also characterized by dermal fibrosis. Mice with a constitutively active TGF β -I receptor were treated with ajulemic acid and were found to have a 30% reduction in dermal fibrosis versus untreated mice.³³ Currently, there are active phase 2 trials with ajulemic acid (JBT-101) in systemic sclerosis and skin-predominant dermatomyositis.

Skin Cancer. Studies using melanoma cell lines have shown some positive results, suggesting a therapeutic potential of THC in the treatment of melanoma. Melanoma transplant studies were carried out in 2 different melanoma cell lines injected into mice treated with THC or vehicle. For one of the melanoma cell lines (B16), THC treatment had no impact on the rate of growth. For the other cell line (Hcmel12), the tumors grew less quickly in mice exposed to THC. The Hcmel12 melanoma cell line is characterized by a protumorigenic inflammatory microenvironment. The THC-treated mice showed a decreased inflammatory response in the tumors, thus explaining the decreased rate of tumor growth.³⁴ In human melanoma, a lack of tumor-infiltrating lymphocytes is actually an indicator of poor prognosis. In another study with the B16 cell line transplanted into mice, they found a decrease in tumor volume, as opposed to no impact in the rate of growth noted in the other study.³⁵

Conclusions. With regard to medical marijuana, whole plant or plant extract, there is a relative paucity of evidence regarding the treatment of skin disease. Even in approved

conditions, many of the approved indications rely on single case reports or circumstantial evidence. The exception is the treatment of pain with medical marijuana, which is supported by several well-designed trials. Regarding the treatment of acne, the only published study we identified with whole cannabis plant extract involved assessing split-face sebum production in 11 normal subjects treated topically and was not double blinded.²⁰ Furthermore, in vitro data actually suggest that the sebum production should be enhanced by THC, and a survey showed increased cannabis use in those with moderate to severe acne. The relevance to patients with acne remains to be seen. The evidence in eczema is largely based on mouse models and uncontrolled human topical studies with synthetic cannabinoid agonists and antagonists, rather than whole-plant extracts.^{26,28,29} The data in systemic sclerosis for ajulemic acid are promising enough that the molecule is now in phase 2 trials for systemic sclerosis and dermatomyositis. The relevance to medical marijuana is unclear given that ajulemic acid is a synthetic derivative without the psychotropic effects and signals through the PPAR- γ pathway.³³ Finally, the data in melanoma are preliminary and should be pursued cautiously given the reduction in tumor-infiltrating lymphocytes. Mouse models in breast cancer and lung cancer showed in vitro antitumor effects, but in vivo models showed increased tumor growth, which is thought to be due to the in vivo immunosuppressive effects of THC.³⁴

Dermatologic Risks Associated With Cannabis Use

Oral Cancers

Considering that most cannabis is consumed by inhaling the smoke, it is not surprising that oral cancers are increased amongst cannabis users. Cannabis smoke contains benzopyrene, nitrosamines, and aromatic hydrocarbons, which are all known carcinogens.^{36,37} These carcinogens promote dysplastic changes within the epithelium, leading to oral premalignant lesions such as leukoplakia and erythroplakia.³⁸ The proposition that cannabis use increases the risk of oral cancers came from several case reports.³⁶ In a retrospective case-control study, there was a 2.6-fold increase in the risk of head and neck cancer.³⁹ This risk increased with increasing frequency and duration of cannabis use. Tobacco use acted in a synergistic manner and increased the risk of cancer 10 to 36 fold.³⁹ In a recent pooled analysis of 9 case-control studies from the United States and Latin America, it was found that cannabis smokers had an odds ratio of oropharyngeal cancer of 1.24 compared with those who had never smoked cannabis.⁴⁰ Interestingly, this pooled analysis found that tongue cancer risk was decreased amongst cannabis users. This may be explained by the fact that the cannabinoids in cannabis have a potential antiproliferative effect.⁴¹ The balance between the carcinogenic and antiproliferative properties of cannabis smoke may also explain

why there have been reports that have found little or no association between cannabis use and oral cancers.^{42,43} The immunosuppressive effects of some cannabinoids and increased HPV exposure may also play important roles in the association of cannabis and the development of oropharyngeal cancers.^{40,44,46} Physicians should examine the oral cavity of cannabis users and biopsy suspicious lesions promptly as the long-term prognosis for younger patients with cannabis-associated oropharyngeal cancers is poor.³⁷

Oral Stomatitis and Candidiasis

While the development of oral cancer is perhaps the most dangerous oral consequence of cannabis use, other effects have been noted in the oral cavity. Acute changes associated with cannabis use include erythema secondary to mucosal irritation, superficial anesthesia, and xerostomia.^{44,47} Chronic changes of cannabis use include chronic inflammation, hyperkeratosis, and leukoplakia.^{36,38,47} These acute and chronic effects of cannabis use can also cause increased tooth decay, increased dental caries, and gingivitis.^{38,44,47} Cannabis users also have a higher prevalence and density of candida and an increased risk of oral candidiasis.⁴⁸

Cannabis Arteritis

Arteritis from cannabis use was first described in 1960. Since then, more than 80 patients with cannabis arteritis have been reported.⁴⁹ The first reports involved Moroccan men smoking kif, a sifted form of cannabis.⁵⁰ The vast majority of patients with cannabis arteritis are young men who regularly smoke cannabis, with at least 1 joint consumed per day.^{49,51} Furthermore, the majority of patients also report concomitant tobacco consumption.⁴⁹ Cannabis arteritis should be on the differential diagnosis for all young men with peripheral necrosis. Generally, the lower extremities are affected more than the upper extremities, and claudication and Raynaud's phenomenon may precede the development of digital necrosis and ulcers.^{49,51,52} Occasionally, venous thrombosis has been associated with cannabis arteritis.⁵² Cannabis arteritis can be differentiated from peripheral arterial disease by duplex ultrasound, where peripheral arterial disease shows calcified plaques or atherosclerosis, while cannabis arteritis shows occlusion of the peripheral arteries. Biopsy of cannabis arteritis is not recommended as it may worsen the arteritis. The initial treatment of cannabis arteritis is to discontinue all cannabis and tobacco consumption.⁵³ Without cannabis cessation, more than 50% of patients had to undergo a limb amputation.⁴⁹ Medical management of cannabis arteritis is daily aspirin at a dose of 75 to 100 mg.⁵³ In severe cases, iloprost has been used to increase perfusion and promote revascularization.^{54,55}

Cannabis Allergy

Cannabis allergy is a growing problem with wide-ranging manifestations that range from mild urticarial reactions and

pruritus to life-threatening angioedema. The first report of a confirmed cannabis allergy was in 1971 of a 29-year-old woman who developed an anaphylactoid reaction after smoking cannabis with confirmation by scratch testing and passive transfer studies.⁵⁶ Respiratory symptoms are perhaps the most common manifestation of cannabis allergies, as most cannabis is consumed by inhalation. These respiratory reactions include rhinoconjunctivitis, asthma, and angioedema.⁵⁷⁻⁵⁹ In terms of cutaneous manifestations of cannabis allergies, contact dermatitis, urticaria, and pruritus have been reported.⁶⁰⁻⁶² Periorbital erythema and edema can be triggered by airborne cannabis allergens.⁶³ Anaphylaxis has occurred from ingestion of cannabis products.^{63,64} The prevalence of cannabis allergies is likely higher than reported. In one recent study, more than 50% of chronic drug users were identified as being sensitized to cannabis by skin prick testing, and 30% were identified as being allergic by a positive cannabis bronchial challenge.⁶⁵ Furthermore, it appears that cannabis cross-reacts with other allergens, as more than 50% of patients sensitized to tomato or tobacco had a positive cannabis bronchial challenge.^{65,66} The cross-reactivity of cannabis allergens with food allergens has led to the identification of a "cannabis–fruit/vegetable syndrome" where allergies to peach, kiwi, banana, apple, cherry, tomato, and occasionally orange or grapefruit cross-react with a cannabis allergy.^{58,66} A diagnosis of a cannabis allergy is based largely on history. Skin prick testing can be done to help confirm the diagnosis, and specific IgE antibody testing is available. Unfortunately, there is no cure for a cannabis allergy; thus, treatment is mainly centered on avoidance of any further cannabis use.

Acute Generalized Exanthematous Pustulosis and Hair Shaft Abnormalities

While the previous sections discussed more well-documented risks of cannabis, there are 2 initial reports that are worth noting. The first is a report that looked at structural alterations of the hair shaft with chronic drug use.⁶⁷ Using light and electron microscopy, chronic cannabis users were noted to have local node-shaped enlarged areas that were not seen on the hair shafts of normal controls.⁶⁷ Second, there is a report of acute generalized exanthematous pustulosis in a 19-year-old woman associated with cannabis use.⁶⁸ Obviously, these individual reports require further investigation.

Conclusion

Unlike the studies looking at the medical uses of cannabis, the risks and potential side effects of cannabis use have been better documented. Dermatologists should be aware of the potential risks of oral cancers and consider oral examinations in all chronic users of cannabis. Oral stomatitis, candidiasis, and xerostomia are other oral manifestations of cannabis use that may present to dermatologists. Cannabis allergy, as presenting with mild urticarial reactions and pruritus to life-threatening

angioedema, will undoubtedly be a growing concern with increased cannabis use. Finally, cannabis arteritis, as noted by digital necrosis and ulcers, is of particular concern in the acute setting, as it has the potential to lead to loss of limbs. It is important that dermatologists familiarize themselves with these manifestations of cannabis use, as we will likely see increasing presentations of these in the dermatology clinic.

Author Contributions

Dr Kirchof and Dr Dhadwal had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Dr Kirchof and Dr Dhadwal. *Analysis and interpretation of data:* Dr Kirchof and Dr Dhadwal. *Drafting of the manuscript:* Dr Kirchof and Dr Dhadwal. *Critical revision of the manuscript for important intellectual content:* Dr Kirchof and Dr Dhadwal. *Statistical analysis:* Dr Kirchof and Dr Dhadwal. *Obtained funding:* None reported. *Administrative, technical, or material support:* None required. *Study supervision:* Dr Kirchof and Dr Dhadwal.

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